quately curtailed by the fluoroquinolone alone [3,11]. Based on our findings, ticarcillin–clavulanic acid and piperacillin–tazobactam should be further evaluated in combination with moxifloxacin against *S. maltophilia* in in vitro synergy studies, animal models and clinical trials.

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Bactericidal activity in cerebrospinal fluid by treating meningitis caused by *Stomatococcus mucilaginosus* with rifampicin, cefotaxime and vancomycin in a neutropenic child

P.G. Skogen[1], *S. Kolmannskog*[1] *and K. Bergh*[2,3,*]

[1]Department of Pediatrics, University Hospital of Trondheim, [2]Department of Microbiology, N-7006 University Hospital of Trondheim, and [3]Department of Laboratory Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[*]Tel: +47 7386 7470 Fax: +47 7386 7765 E-mail: kare.bergh@medisin.ntnu.no

Accepted 4 October 2000

Stomatococcus mucilaginosus is part of the normal oropharyngeal flora. Since the first report of *Stomatococcus mucilaginosus* as a human pathogen in 1978 [1], this microorganism has been increasingly reported to cause serious infections in immunocompromised patients. The majority of infections reported are septicemia, catheter-related infections, meningitis and endocarditis [2–5]. Neutropenia after chemotherapy for malignant disease appears to be the most frequent predisposing condition [2,3,6–9].

Although *Stomatococcus mucilaginosus* is usually susceptible to several antibiotics, the choice of treatment for central nervous system (CNS) infections is complicated. Goldman et al found in a review of 13 patients with meningitis due to *Stomatococcus mucilaginosus* that various treatment strategies were employed

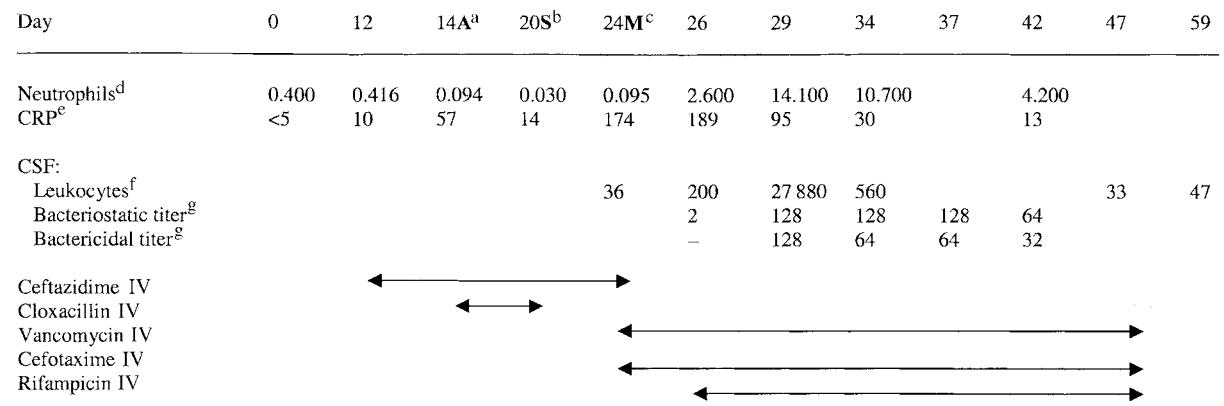

Figure 1 Overview of relevant parameters and therapy for *Stomatococcus mucilaginosus* septicemia and meningitis after onset of chemotherapy for acute lymphoblastic leukemia. [a,b,c]Time of diagnosis of: A abscess, S septicemia, M meningitis. [d]Neutrophils $\times 10^9$/L. [e]C-reactive protein mg/L. [f]Leukocytes in CSF $\times 10^6$/L. [g]Titer: reciprocal of the dilution of CSF with bacteriostatic and bactericidal effect, respectively.

[10]. Vancomycin intrathecally was employed in five of these cases. We are not aware of reports considering the pharmacodynamic properties of the antibiotics employed for meningitis caused by *Stomatococcus mucilaginosus*. We report here the achievement of adequate bactericidal cerebrospinal fluid (CSF) levels of antibiotics by adding rifampicin to an intravenous regimen of cefotaxime and vancomycin, which by itself was inadequate.

A 2.5-year-old boy with a diagnosis of acute lymphoblastic leukemia (pre-B ALL, intermediate risk) was started on chemotherapy through a Hickman central venous catheter consisting of prednisolone orally, weekly intravenous vincristine and intravenous adriamycin on day 0 during the induction phase, according to the Nordic ALL protocol [11]. An overview of relevant parameters and antibiotic therapy is given in Figure 1. From day 6, the patient was severely neutropenic and thrombocytopenic. On day 12, he was febrile, and cloxacillin (25 mg/kg four times a day) and ceftazidime (33 mg/kg three times a day) were started intravenously. Pus at the insertion site of the Hickman catheter and several blood cultures grew β-lactamase-producing *Staphylococcus aureus.* On this regimen, the patient improved rapidly, with normalization of fever and C-reactive protein. On day 20, while still on therapy with ceftazidime and cloxacillin, he became septic, with a temperature above 41 °C. Oral mucositis was present clinically. The Hickman catheter was removed on day 22. Four blood cultures obtained on day 20 grew *Stomatococcus mucilaginosus,* whereas *Staphylococcus aureus* grew from the Hickman catheter. *Stomatococcus mucilaginosus* was identified by API ID32 Staph (identification profile 077175210) and by conventional methods (Gram-positive cocci in clusters and tetrads, weakly catalase-positive colonies that adhered strongly to the agar surface, failure to grow on agar supplemented with 5.0% NaCl, presence of mucoid capsule, pyrrolidonyl arylamidase (PYR) positive, esculin hydrolysis and leucine aminopeptidase (LAP) positive). The organism grew poorly on Mueller–Hinton agar but well on nutrient agar (Blood Agar Base, Difco, Detroit, MI, USA). Cloxacillin was substituted with vancomycin (17 mg/kg three times a day). On day 24, meningitis was suspected, and CSF analysis showed 36×10^6 leukocytes/L, glucose 2.2 mmol/L and protein 0.44 g/L. A Gram stain of CSF revealed a high number of Gram-positive cocci in pairs, tetrads and clusters, while an India Ink wet mount demonstrated microaggregates of encapsulated cocci (Figure 2). Culture of CSF yielded growth of *Stomatococcus mucilaginosus*. Cefotaxime (62.5 mg/kg four times a day) replaced ceftazidime for therapy of meningitis in combination with intravenous vancomycin. A repeat CSF analysis on day 26 showed 200×10^6 leukocytes/L, glucose 0.2 mmol/L and protein 2.2 g/L. Numerous cocci were observed on a Gram stain, and culture again yielded growth of *Stomatococcus mucilaginosus*. From day 26, intravenous rifampicin (7 mg/kg three

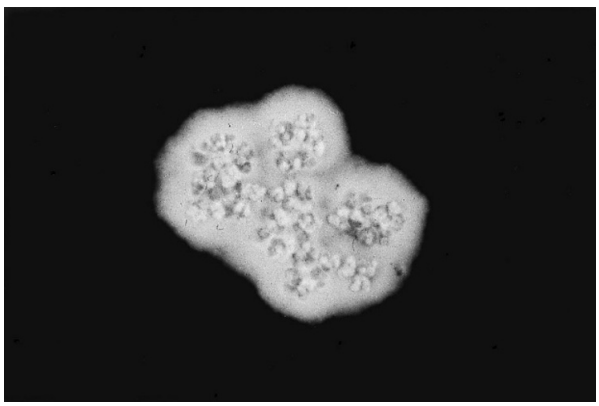

Figure 2 Wet mount (India Ink) of cerebrospinal fluid showing aggregates of encapsulated *Stomatococcus mucilaginosus.* Magnification × 1000.

times a day) was added to the antibiotic regimen. Susceptibility testing by E-test showed the following minimum inhibitory concentrations (MICs): penicillin G 2.0 mg/L, cefotaxime 2.0 mg/L, ceftazidime 8.0 mg/L, ceftriaxone 0.75 mg/L, vancomycin 1.5 mg/L, imipenem 0.25 mg/L and rifampicin <0.002 mg/L. Bacteriostatic assay of CSF was performed in microtiter plates using a modification of MIC determination as described by Tamashiro [12], with 5×10^5/mL of the clinical *Stomatococcus mucilaginosus* isolate as inoculum and twofold dilution of CSF as antibiotic source; the wells were read after both 24 and 48 h of incubation. After 48 h of incubation, the number of colony-forming units (CFUs) was determined in wells with no visible growth. A greater than 99.9% reduction of viable bacteria was considered significant for bactericidal activity. CSF analysis on day 26 revealed bacteriostasis only in undiluted CSF, with no bactericidal effect. On day 29, the bacteriostatic and bactericidal titers in CSF were 128 after 48 h. This and all subsequent CSF cultures were sterile. The patient's temperature and CRP normalized. A few days after the onset of meningitis, hematopoiesis recovered and leukocytosis ensued, both peripherally and especially in the CSF. After an initial slight improvement, the patient again became comatose on day 32, with positive Babinski signs on the left side. A CT scan revealed increased intracranial pressure with hydrocephalus, necessitating external drainage of CSF, and later a ventriculoperitoneal shunt was established. The patient did not recover consciousness. EEG was strongly pathologic, and periventricular cerebral necrosis was demonstrated on a CT scan. On day 63, both antibiotic and antileukemic therapy were stopped because of irreversible brain damage. Bone marrow examinations had shown complete remission of the leukemia. The patient died on day 74. Postmortem examination of CSF was sterile. An autopsy was denied.

DISCUSSION

This case presents the typical hallmarks of an infection due to *Stomatococcus mucilaginosus*, i.e. a severely neutropenic patient in whom septicemia and subsequently CNS involvement develops. In the first CSF specimen, microorganisms were present in high numbers, whereas leukocytes were virtually absent. This would indicate that the meningitis had developed over several days while the patient was neutropenic and receiving ceftazidime and vancomycin. Complications occurring after or while receiving apparently appropriate chemotherapy for *Stomatococcus mucilaginosus* bacteremia have been described by others [13,14]. It is noteworthy that the clinical signs of meningitis/meningoencephalitis worsened as the bone marrow recovered, with subsequent influx of neutrophils into the meninges and brain. It is reasonable to assume that the inflammatory response elicited by the pronounced influx of leukocytes into the brain is responsible for the brain damage occurring after the initial improvement. The infection itself was cleared, as several CSF analyses demonstrated sterilization after rifampicin was commenced and after therapy was discontinued.

We demonstrated that adequate bacteriostatic and bactericidal levels of antibiotics in CSF were achieved by the addition of rifampicin to an antibiotic regimen of intravenous cefotaxime and vancomycin. With this regimen, sufficiently high bactericidal titers, i.e. 128 initially, were obtained and the infection was cleared. The initial treatment with vancomycin and cefotaxime was insufficient, probably due to the low sensitivity of this strain of *Stomatococcus mucilaginosus*. MICs for penicillin and cefotaxime were eight times higher than those observed by von Eiff et al in an vitro study including 63 strains [15]. The vancomycin concentration in CSF was determined only on days 9 and 14 after the onset of meningitis, and was as low as 3.7 and 2.7 mg/L, respectively. This supports our assumption that rifampicin was mainly responsible for establishing adequate bactericidal concentrations in CSF, possibly in conjunction with the other antibiotics employed. The extremely low MIC of rifampicin of this isolate and the favorable properties of rifampicin in achieving high concentrations in CSF [16] suggest a role for rifampicin in the treatment of meningitis caused by *Stomatococcus mucilaginosus*, particularly if the use of intrathecal administration of vancomycin is not feasible or otherwise contraindicated.

Our pharmacodynamic data from this patient demonstrate that by adding rifampicin to an intravenous regimen of vancomycin and cefotaxime, adequate bactericidal and bacteriostatic levels of antibiotics in CSF were achieved. In conclusion, we recommend that rifampicin be considered a primary drug in meningitis caused by *Stomatococcus mucilaginosus* in neutropenic patients.

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Nasopharyngeal carriage of penicillin-resistant, macrolide-resistant and multiply-resistant *Streptococcus pneumoniae* in day-care centers in Sofia, Bulgaria

R. Markovska, T. Strateva, G. Gergova and E. Keuleyan*

Department of Microbiology, Medical University, 2, Zdrave str, Sofia 1431, Bulgaria

*Tel: + 359 2 51 66 627 Fax: + 359 2 952 0345 E-mail: keuleyan@medfac.acad.bg

Accepted 4 October 2000

A significant increase of penicillin-resistant, macrolide-resistant and multiply-resistant *Streptococcus pneumoniae* has been observed worldwide during the last 10–15 years [1]. Resistant strains have become a challenge in the treatment of community-acquired pneumonia, meningitis, sinusitis and acute otitis media, where *S. pneumoniae* is one of the leading bacterial pathogens [2]. Nasopharyngeal carriage of *S. pneumoniae* in children from day-care centers has been determined to be an important epidemiologic risk factor [3–7]. Another well-recognized risk factor is the irrational and excessive global usage of antibiotics, particularly the antibiotics prescribed to children, that may select the resistant strains [8–11]. Today, data on different high rates of resistance are available from different countries [4,12–17]. Specialized surveillance programs have been established to minimize the incidence of resistant strains [5,7].

Data on this problem in Bulgaria are available only from children admitted to hospital [18]. In this pilot study, we aimed to evaluate the rate of penicillin-, macrolide- and multiply-resistant *S. pneumoniae* from nasopharyngeal carriage in day-care centers and to look for any correlation with the antibiotic usage that might promote their incidence.

We studied 152 children from three different day-care centers, located in different regions of Sofia. The age of the children was from 1 to 6 years (mean 3.8). Nasopharyngeal specimens were obtained during October/November 1999. The swabs were inoculated on blood agar plates and incubated at 37 °C in 5–10% CO_2 for 18–24 h. Identification of *S. pneumoniae* was by the routine criteria: α-hemolytic colonies with typical morphology, which were susceptible to Optochin (Becton Dickinson, BBL, Cockeysville, MD, USA). Susceptibility testing was performed on Mueller–Hinton II agar (Becton Dickinson, BBL), supplemented with 5% sheep blood, according to the NCCLS [19]. In order to test the susceptibility to penicillin, an oxacillin disk, 1 μg, was first applied, and then the strains with